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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,868	05/04/2001	Wei-Qiang Gao	GENENT.035C1	1085

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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/849,868	GAO, WEI-QIANG	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/22/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) *1-12,14-17 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14-17, and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments of 09/22/2006 have been entered in full. Claims 1-12, 14-17, and 19-21 are under examination.
2. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.
4. Applicant's objection to the long delay in prosecution of this application is acknowledged. This examiner has no knowledge of events that occurred prior to the transfer of this application to Art Unit 1647, and can offer no explanation or excuse for the delay. Applicant can be assured that every reasonable effort will be made to move the case expeditiously in the future. It is further agreed that "piece-meal" prosecution is to be avoided as much as possible. Although piece-meal prosecution is regrettable, when an examiner discerns that patent claims fail to meet the requirements of 35 U.S.C. 112 or are anticipated by prior art, rejections must be made regardless of prior prosecution history.

Claim Rejections - 35 USC § 102

5. Claim 6 remains rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6017886 (Carnahan). As noted in the rejection of record, the recombinant peptide taught in Carnahan is "recombinant human heregulin peptide or fragment thereof" as recited in claim 6. Claim 6 has not been amended.

Claim Rejections - 35 USC § 103

6. Claim 9 remains rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6017886 (Carnahan) in view of US Patent 5587458 (King). Applicant's amendments have not altered the recitation of agonist antibodies and fragments. Applicant argues that the Carnahan and King references are directed to diametrically opposed goals and therefore there is no reasonable expectation of success in combining them. Specifically, Carnahan is directed to methods of growing cells whereas King is directed to killing cancer cells. It was, however, well known in the art at the time of both the Carnahan and King disclosures that, while NDF/heregulins have been found to be weakly mitogenic for various epithelial cells, certain tumor cells undergo growth arrest in response to NDF/heregulin (see US Patent 5,670,342, of record and cited in Carnahan, at column 2, lines 22-30). One of skill in the art would recognize that the opposite outcomes to which the Carnahan and King patents are directed merely reflect different cellular responses to activation of erbB2/3 receptors. King teaches antibodies that increase tyrosine phosphorylation of erbB2, which is an indication of receptor activation (Example 5, Figure 4B).
7. Claim 11 remains rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6017886 (Carnahan), in view of Carraway *et al.* Neither claim 11 nor claim 6, from which claim 11 depends, has been amended. Applicant argues that Carraway does not provide suggestion or motivation to use rHRG-β1-177-244 on inner ear cells. It is Carnahan that provides motivation and suggestion to activate the erbB2/3 receptors in inner ear cells. Further, although Carnahan indicates that a particular engineered peptide has superior

activity, Carnahan also teaches that many heregulin peptides are effective in stimulating utricular sensory epithelial cells (see figures 3 and 5). Carraway teaches that rHRG-β1-177-244 is an effective activator of erbB2/3. Therefore one of skill in the art would expect to be able to successfully stimulate proliferation of inner ear epithelial cells with rHRG-β1-177-244.

8. Claims 1-5, 7,8, 10-12, 14-17, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6017886 (Carnahan), in view of U.S. Patent 5,367,060, issued November 22, 1994 ('060). In response to the prior rejection of these claims a being anticipated under 35 U.S.C. 102(e) as being anticipated by Carnahan, Applicant argues that highly active recombinant peptide taught by Carnahan does not comprise amino acids 226 to 266 and therefore Carnahan does not anticipate the amended independent claims. However, contrary to Applicant's assertion, Carnahan does discuss heregulin-α and heregulin-β1. Carnahan teaches that many heregulin peptides, including heregulin-α and heregulin-β1 (termed NDFs by Carnahan) and GGF are effective in stimulating utricular sensory epithelial cells (see figures 3 and 5; column 9, lines 55-60). The heregulin peptides exemplified in Carnahan did not include all of amino acids 226 to 266; for heregulin-α and heregulin-β1 the C-terminal amino acid corresponds to position 241 (like heregulin-β3; see Example 2 of Carnahan). In view of these teachings, it would be obvious to the skilled artisan that any heregulin peptide that retains a significant portion of the EGF-like domain can stimulate utricular sensory epithelial cells. The'060 patent discloses the full amino acid sequences of Hrg-α, Hrg-β1, Hrg-β2, Hrg-β2-like, and Hrg-β3 heregulin peptides; see Figure 15, which is identical to Figure 6 of the instant application. The '060 patent teaches the domains of each

heregulin peptide that are responsible for binding to receptor at column 8, lines 42-50; these teachings at least render the HRG-β1-177-244 fragment of instant claim 11 obvious. The'060 patent identifies fragments comprising amino acids 226-265 of both Hrg-α and Hrg-β as being preferred ligands with receptor binding affinity (column 16, lines 7-18). Therefore, the instantly claimed polypeptides and fragments were well known to be capable of activating receptors at the time the instant invention was made. It would be obvious to one of skill in the to use any of them to stimulate utricular sensory epithelial cells, as shown by Carnahan.

Claim Rejections - 35 USC § 112

9. Claims 1-5, 7-12,14-17 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation "said fragments comprise amino acids numbered 226 to 266 of the corresponding heregulin sequence" in independent claims 1, 14, and 16, is unclear because the antecedent for "said fragments" includes antibody fragments. Thus, the claim appears to encompass antibodies that comprise heregulin sequences. This could be clarified by amendment to recite "said heregulin fragments".
10. The limitation "said fragments comprise amino acids numbered 226 to 266 of the corresponding heregulin sequence" is additionally unclear for the following reasons. SEQ ID NO:1 and SEQ ID NO:3 depict amino acid sequences deduced from the open reading frames of encoding cDNAs, and therefore they include 44 and 30 N-terminal amino acids prior to the initiator methionine, respectively. Consequently, "226 to 266" has a different meaning

with respect to structural/functional domains (such as the EGF-like domain responsible for binding to receptors) in these sequences relative to each other and relative to SEQ ID NOS: 5, 7, and 9, which do start with methionine. The "226 to 266" limitation makes no sense as it refers to heregulin-β3 (SEQ ID NO:7), which has only 241 amino acids. "226 to 266" has yet another meaning in the sequence of γ-heregulin (SEQ ID NO: 11), which comprises 768 amino acids. The amino terminus of γ-heregulin is radically different from all other forms of heregulin; the EGF-like domain is near the C-terminus and is apparently identical to that of heregulin-β3, thus lacking amino acids corresponding to positions 241-266 of HRG-β2. The recitation of rHRG-β1-177-244 in claim 11, and indeed all recitations of specific amino acid positions, are unclear as they refer to SEQ ID NOS: 1 or 3. The specification does not clarify the issue, as the discrepancy is found throughout the specification. The specification cites specific positions within HRG-α and HRG-β1, which may be understood with reference to Figures 1,2, and 6, and the prior art, but are ambiguous because of their definitions in SEQ ID NOS: 1 and 3. For example, section [0157] of the published application cites S177 of HRG-β1, whereas position 177 in SEQ ID NO:3 is a tyrosine. Thus, a literal interpretation of these claims yields a result that conflicts with the specification as a whole and with the state of the art at the time of filing. Logically, one of skill in the art would expect that the "226 to 266" limitation is meant to describe a domain that is conserved among the recited forms of heregulin. It is suggested that submission of new sequences depicting only translated sequences and amending the specification accordingly would not necessarily constitute new matter, in view of Figures 1,2, and 6, and would greatly facilitate clarification of the claims.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D.,whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
19 December 2006

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